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LÝÐVELDIÐ ÍSLAND

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(71)	*Umsækjandi* Applicant(s)	**Actavis group**
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EINKALEYFASTOFAN

Reykjavík, 13. apríl 2005

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Formulations of ramipril and piretanide

FIELD OF THE INVENTION

The present invention relates to a stable pharmaceutical formulation of ramipril and piretanide.

TECHNICAL BACKGROUND AND PRIOR ART

Ramipril, (2*S*,3*aS*,6*aS*)-1[(*S*)-*N*-[(*S*)-1-carboxy-3-phenylpropyl] alanyl] octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid, 1-ethyl ester is an angiotensin converting enzyme (ACE) inhibitor. Ramipril is used for the treatment of hypertension, heart failure, stroke, myocardial infarction, diabetes and cardiovascular disease.

Ramipril and the acid form, ramiprilat, is described in EP 0 097 022 B1.

Piretanide is described in US 4,010,273.

Compositons of ramipril and piretanide is described in EP 215 357 B1. Calcium sulfate is mentioned in this patent.

The preparation of stable pharmaceutical formulations of ramipril is complicated since it is susceptible to certain types of degradation. Ramipril can undergo cyclization via internal nucleophilic attack to form substituted diketopiperazines and also degrade via hydrolysis and oxidation.

EP 1 501 546 A1 describes stable pharmaceutical formualtion for combinations of a statin and an ACE inhibitor. The problem underlying the invention is that if an ACE inhibior is in the presence of a stabilised statin, the ACE inhibitor decomposes to such extent that even after short storage period the content of decomposition products exceeds the permissible limit of degratation. The invention provides a formulation wherein the statin and the

ACE inhibitoer are separated by physiologically acceptable inert material. Calcium sulfate is mentioned as a possible inorganic filler but it is neither claimed nor mentioned in any examples. In fact all the examples are concerned with three-layer tablet, wherein the statin layer and ACE inhibitor layer are seperated by a layer of microcrystalline cellulose. The combination of the ACE inhibitor with a diuretic is not mentioned.

EP 0 280 999 B1 describes a composition comprising ACE inhibitor (i.e. ramipril), an alkali or alkaline earth metal carbonate and saccharide wherein the ACE inhibitor is stabilized against degradation (cyclization, discoloration and hydrolysis) by means of the other mentioned ingredients. In the specifications the relevant saccharides are lactose and mannitol. Modified starch is mentioned as disintegrant in the specification.

EP 0 317 878 B1 claims a stable, compressed pharmaceutical formulation containing a compound of a defined formula (i.e. ramipril) wherein, for stabilization before compression, a compound of the formula is a) coated with a polymeric, physiologically tolerated protective coating, or b) mixed with a physiologically tolerated buffer which ensures that a pH in the weakly acidic to weakly alkaline range is set up in a pharmaceutical formulation in the presence of moisture, where sodium bicarbonate is excepted as buffer, or c) mixed with a physilogically tolerated buffer which ensures that a pH in the weakly acid to weakly alkaline range is set up in a pharmaceutical formulation in the presence of moisture, and is coated with a polymeric, physiologically tolerated protective coating, where, in the case of stabilization according to b) with alkali metal or alkaline earth metal carbonate, the formulation is free of sugar.

SUMMARY OF THE INVENTION

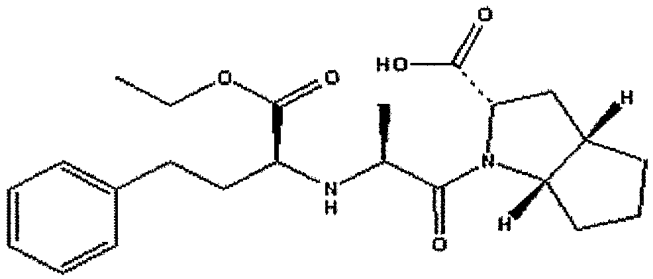
In an attempt to prepare a stable tablet formulation of ramipril, it was discovered that useful formulations can be produced by the use of calcium sulphate dihydrate (e.g. Compactrol) as filler material.

Properties of calcium sulphate are described in A. H. Kibbe, Handbook of pharmaceutical excipients, 73 – 76, American Pharmaceutical Association, Washington, and Pharmaceutical Press, London, 2000.

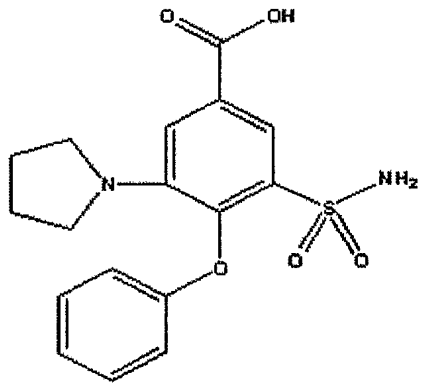
Calcium sulphate dihydrate is known as an inert diluent in compressed tablets. However, it was surprising that the stability of the tablets proved to be very satisfying.

DETAILED DESCRIPTION

The invention provides a pharmaceutical formulation comprising ramipril,



piretanide,



Compactrol as filling agent, and sodium hydrogen carbonate as stabilation agent.

The pharmaceutical formulation of the present invention comprises typically:

a) 0.1 – 5.0% w/w of ramipril;

b) 1.0-7.0% w/w piretanide;

b) 55 - 95% w/w of Compactrol;

c) 0.1 – 5.0% w/w of sodium hydrogen carbonate;

and optionally disintegrant (e.g. starch), binder and/or lubricant (e.g. sodium stearyl fumarate).

For the tablet formulation containing 5 mg ramipril and 6 mg piretanide, the preferred amount of ramipril is 1.5 – 2.5% w/w, the amount of piretanide is 1.8 – 3% w/w, the amount of Compactrol is 65-85% w/w, the amount of sodium hydrogen carbonate is 3-5% w/w, the amount of starch pregelatinised is 10-20% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

Since ramipril is susceptible to certain types of degradation, there are several impurities formed during the manufacturing process and storing of the tablet. It is of high importance to minimize this degradation. The strength of different exipients was adjusted until a useful formulation was found.

There are certain criterias that these componds are not allowed to exceed. The present formulation has proved to be stable.

Ramipril diketopiperazine is one of the compounds formed via degradation. The present formulation proved to be especially stable with regard to formation of the diketopiperazine.

EXAMPLES

The following example is merely illustrative of the present invention and it should not be considered as limiting the scope of the invention.

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Example 1

Formulation for 5/6 mg ramipril piretanide tablets

Ramipril	1.9% w/w
Piretanide	2.3% w/w
Compactrol	76 % w/w
Sodium hydrogen carbonate	3.7% w/w
Starch pregelatinised	15% w/w
Sodium stearyl fumarate	1% w/w

CLAIMS

1. A tablet formulation comprising:

a) 0.1 – 5.0% w/w of ramipril;

b) 1.0-7.0% w/w piretanide;

b) 55 - 95% w/w of Compactrol;

c) 0.1 – 5.0% w/w of sodium hydrogen carbonate;

optionally in combination with a disintegrant, binder and lubricant and other excipients.

2. The tablet formulation of claim 1, wherein the calcium sulphate dihydrate is Compactrol.

3. The tablet formulation of any of claims 1 to 2, wherein the disintegrant and binder is pregelatinised starch.

4. The tablet formulation of any of claims 1 to 3, wherein the lubricant is sodium stearyl fumarate.

5. The tablet formulation of the preceding claims containing 5 mg ramipril and 6 mg piretanide, the preferred amount of ramipril is 1.5 – 2.5% w/w, the amount of piretanide is 1.8 – 3% w/w, the amount of Compactrol is 65-85% w/w, the amount of sodium hydrogen carbonate is 3-5% w/w, the amount of starch pregelatinised is 10-20% w/w and the amount of sodium stearyl fumarate is 0.5-1.5% w/w.

ABSTRACT

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EP 0 317 878 B1 claims a stable, compressed pharmaceutical formulation containing a compound of a defined formula (i.e. ramipril) wherein, for stabilization before compression, a compound of the formula is a) coated with a polymeric, physiologically tolerated protective coating, or b) mixed with a physiologically tolerated buffer which ensures that a pH in the weakly acidic to weakly alkaline range is set up in a pharmaceutical formulation in the presence of moisture, where sodium bicarbonate is excepted as buffer, or c) mixed with a physilogically tolerated buffer which ensures that a pH in the weakly acid to weakly alkaline range is set up in a pharmaceutical formulation in the presence of moisture, and is coated with a polymeric, physiologically tolerated protective coating, where, in the case of stabilization according to b) with alkali metal or alkaline earth metal carbonate, the formulation is free of sugar.

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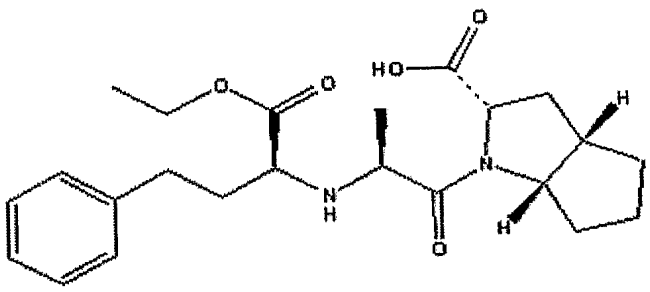
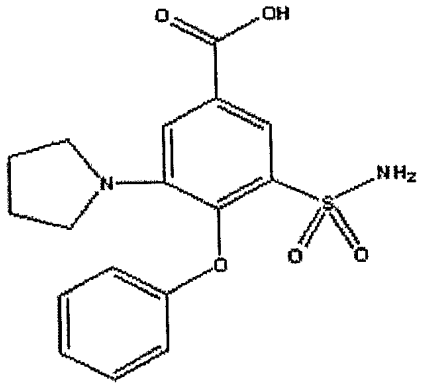


piretanide,



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